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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/614,498	07/07/2003	Alan P. Kozikowski	GUX-012.01	8108

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EXAMINER	
DESAI, RITA J	

ART UNIT	PAPER NUMBER
1625	

MAIL DATE	DELIVERY MODE
12/04/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/614,498	KOZIKOWSKI ET AL.	
	Examiner	Art Unit	
	Rita J. Desai	1625	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11/25/09*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-8,32,41,50,60-62,64,73-81 and 90-94* is/are pending in the application.

4a) Of the above claim(s) *41, 50, 60-62, 64, 73-81, 90-91* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8,32 and 92-94* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 11/25/09 has been entered.

Claims 1-8, 32, 41, 50, 60-62, 64, 73-81, 90-94 are pending.

Claims 1-8, 32, 92-93 and stand rejected.

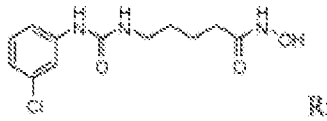
New Claim 94 has been added.

Claims 41, 50, 60-62, 64, 73-81, 90-91 are withdrawn .

The claims were rejected under 35 USC 103 and 35 USC 112 and they still stands.

Response to the arguments:-

The Examiner maintains the rejection of claims 1-8 and 32, 92-94 as being allegedly unpatentable under 35 U.S.C. 103(a) over Richon et al. Proc. Natl. Acad. Sci. Vol. 95, pp. 3003-7 (1998) ("Richon") and WO0226696 to Watkins et al. ("Watkins"). The Examiner also refers to Jung et al.1997, 1999. The Examiner contends that Richon discloses the following compound:



Richon compound 7, 3-Cl-UCHA,

Applicants submit that the Examiner has not established any of the aforementioned criteria. First, the Examiner has failed to provide a reasoned identification of a lead compound. Richon describes hybrid polar compounds ("HPC's") which inhibit HDAC. *Richon* at abstract. The compounds Richon describes include SAHA, TSA, 3-C1-UCHA, and several others. *Richon,* Table1. The HPC's of Richon have two amides, two esters, two hydroxamic acids, a hydroxamic

acid and an amide, an amine and a hydroxamic acid, or a urea and a hydroxamic acid. Out of all of these possible choices, the Examiner chooses 3-C1-UCHA, which contains a urea and a hydroxamic acid.The Examiner points to no rationale in any cited references for selecting this compound over all of the others, but rather appears to improperly use Applicant's disclosure as a blueprint for modifying this particular compound of Richon. In fact, according to Richon, TSA is more potent than compound 7. The Examiner has not explained why the skilled artisan would select compound 7 as a lead over TSA, or SAHA or CBHA, for that matter, because Richon provides no such motivation.

Response

Richon discloses several compounds with the urea and the amide linkages and shows the equivalency of the different linkers as given in TSA, SAHA or CBHA or the compound 7.

The reference clearly teaches that compound 7 has the most potency HPC in T24 and ARP-1 cells, human bladder cell lines and induce apoptosis of the human myeloma cell lines.

See page 3005 , paragraph above the letter "A".

Effect of HPCs on Histone Acetylation Levels in T24 and ARP-1 Cells. In addition to MEL cells, HPCs induce differentiation of the human bladder carcinoma cell line T24 (3) and induce apoptosis of the human myeloma cell line ARP-1 (4). We determined the effect of HMBA, the second-generation HPC 3-Cl-UCHA (Table 1, compound 7), and TSA on the accumulation of acetylated histone H4 in T24 and ARP-1 cells. 3-Cl-UCHA is the most potent HPC in T24 and ARP-1 cells.

This is motivation enough to pick compounds that would be similar to the compound 7 in the reference.

M. Jung et al on page 10 of WO 02/26696 (Watkins et al) teaches the mode of activity , with a binding region a spacer and an enzyme inhibiting group.

Thus Richon discloses the compound 7 showing that it is more potent , (an urea linkage, same as that of the applicants) motivating a person of skill in the art to modify the compound and make a homolog with an addition CH2 to link the phenyl ring.

WO 02/26696 teaches several linkages and the that the phenyl ring does not have to be directly linked. The fact that Watkins teaches s many different linkages modifying the compound 7 of Richon by a (CH2) Benzyl v a phenyl is prima facie obvious especially since Richon teaches that the compound 7 is more potent.

Thus the rejection of claims 1-8, 32, 92-93 over Richon still stands

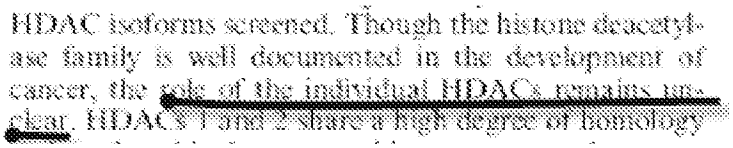
The rejection of the claims 1-8, 32, under 35 USC 112 over scope of enablement also still stands.

Applicants are arguing that the fact that it is difficult does not necessarily make it non enabled. Yes but it would require an undue amount of burden to make and use the invention as claimed. Applicants are arguing a homolog difference to be not prima facie and at the same time saying that any heterocyclic group for R1 would also work. The examiner finds these arguments very contradictory.

Applicants have failed to show the starting material for the various heterocyclic groups. Some definition and description is given , how ever a very general scheme scheme 1 is given with R1 (CH2)m-NH2 as a starting material. when you consider heterocyclic groups (which may further be substituted) the reaction does not provide for the various protection of the different groups.

Applicants argue that regarding the 3rd and 5th wands factor contain several erroneous legal standards is incorrect. Applicants argue that they are not required to disclose every species encompassed by the claim even in unpredictable art is incorrect. When the art is highly unpredictable where the prior art does not have the urea compounds with the R1 as heteroring applicant should show a reduction to practice of atleast one from each grouping. The examiner

has clearly made a prima facie case . See Methot et al which states that the role of individual HDAC's remains unclear.


HDAC isoforms screened. Though the histone deacetylase family is well documented in the development of cancer, the role of the individual HDACs remains unclear. HDACs 1 and 2 share a high degree of homology

Siliphaivanh 2007 also shows the unpredictability of not just the groups but even small substitutions such as nitrile and methoxy on the phenyl group let alone the position at which it was substituted.

Also see Siliphaivanh 2007, page 4621

Encouraged by the activity of benzamide **5a**, our attention was directed toward the synthesis of analogues with diverse substitution around the phenyl ring in the surface recognition domain. Representative analogues (Table 1) demonstrate that a wide array of functionality can be tolerated in the malonyl–phenyl rings including nitrile, methoxy, and morpholine moieties. A reduction in cellular potency can be seen in biaryl **5i**, possibly due to its low hydrophilicity. The clog P^{23} of **5i** is greater than that of the phenyl amide **5a** by two log units. Notably, ortho-substitution of the malonyl–phenyl rings was tolerated in contrast to ortho-substitution of the phenyl ring within vorinostat, which leads to a marked decrease in activity.

Moreover, both amide NH moieties were essential for significant enzymatic and cellular potency (Table 2). Incorporation of a single methyl group on the malonyl sidechains to give **5j** resulted in a 5-fold loss of potency. Similarly, the dimethyl derivative **5k** was 100-fold less potent indicating that hydrogen bonding, either inter- or intra-molecular, may play an important role in the recognition of the HDAC active site. Similarly, it was shown that malonyl di-ester analogues possessed significant reduction in HDAC enzymatic activity as well (data not shown).

So the examiner has made a prima facie case and applicants have failed to show that their compounds are enabled to make and how to use them.

Conclusion

Claims 1-8, 32, 92-94 are under examination.

Claims 41, 50, 60-62, 64, 73-81, 90-91 are withdrawn as being non-elected.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Rita J. Desai whose telephone number is 571-272-0684. The examiner can normally be reached on Monday - Friday, flex time..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet Andres can be reached on 571-272-0867. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Rita J. Desai/
Primary Examiner, Art Unit 1625

December 1, 2009.